UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:			
Thomas W. Dubensky Jr. et al.		Art Unit:	1645
Appln. No.:	10/773,618	Examiner:	GRASER, Jennifer E.
Filed:	Feb. 6, 2004	Atty. Docket:	ANZ-1200-UT
For:	*Modified Free-Living Microbes, Vaccine Compositions and Methods of Use Thereof*	Confirm. No.:	8471

APPEAL BRIEF

Commissioner for Patents
Mail Stop Appeal Brief
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

In response to the final Office Action dated May 9, 2009 and subsequent to the Notice of Appeal filed on November 2, 2009, Applicants submit the following Appeal Brief.

CERTIFICATE OF TRANSMITTAL UNDER 37 C.F.R. 1.8

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being electronically filed via EFS-Web at the United States Patent and Trademark Office, on the date shown below.

21 April 2010
Date of Deposit

/Kristen Lemme/
Kristen Lemme

Table of Contents

Table of Authorities

Real Party in Interest

The real party in interest in the case is Aduro Biotech, the assignee of record.

Related Appeals and Interferences

As of the filing date of this appeal brief there are no other appeals or interferences related to this case.

Status of the Claims

Claims 20-21, 87, 106, 110-113, 118, 137, 141-147 are rejected and under appeal.

Claims 1-19, 22-86, 88-105, 107, 109, 114-117, 119-136, 138, 140, and 148-189 are canceled. Claims 108 and 139 are withdrawn.

Status of Amendments

No amendments were filed after final rejection.

Summary of Claimed Subject Matter

The claimed invention provides a method of preventing or treating a disease in a host (specification, p. 5, lines 4-5); and a method for inducing an immune response in a host to an antigen (p. 4, lines 18-21). In each case, the methods rely on expression of a polypeptide of interest from an attenuated *Listeria monocytogenes* bacterium comprising: psoralen-induced intrastrand crosslinks within the bacterial genome which inhibit replication of the bacterium (specification, p. 3, lines 26-27; p. 4, lines 4-6; p. 43, lines 24-26); and mutations in the *uvrA* and *uvrB* genes which inhibit the ability of the bacterium to repair those crosslinks (specification, p. 4, lines 11-13; p. 53, lines 21-23). This combination can increase the safety and effectiveness of using a bacterium as a vaccine platform in a host (specification, p. 6, lines 17-28; page 29, lines 12-20; page 34, lines 11-13).

Independent claim 20 and its dependent claims provide a method of preventing or treating a disease in a host (specification, p. 5, lines 4-5). The methods involve administering to

the host an effective amount of a vaccine (specification, p. 5, line 5). The vaccine can comprise a modified *Listeria monocytogenes* bacterium (specification, p. 5, lines 20-22). The modified bacterium can comprise psoralen-induced interstrand crosslinks introduced between the strands of genomic DNA double helix (p. 3, lines 26-27; p. 4, lines 4-6; p. 43, lines 24-26). The interstrand crosslinks inhibit replication of the modified bacterium (p. 3, lines 27-28). The modified bacterium also has one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of said interstrand crosslinks (p. 53, lines 21-23). The modified bacterium further has a nucleic acid sequence encoding a polypeptide heterologous to said *Listeria monocytogenes* bacterium operably linked to a promoter sequence directing expression of the heterologous polypeptide by the modified bacterium (p. 98, lines 1-8).

In another embodiment of the present invention, independent claim 21 and its dependent claims provide a method of inducing an immune response in a host to an antigen (p. 4, lines 18-21). The methods involve administering to the host an effective amount of a vaccine (specification, p. 5, line 5). The vaccine can comprise a modified *Listeria monocytogenes* bacterium (specification, p. 5, lines 20-22). The modified bacterium comprises psoralen-induced interstrand crosslinks introduced between the strands of genomic DNA double helix (p. 3, lines 26-27; p. 4, lines 4-6; p. 43, lines 24-26). The interstrand crosslinks inhibit replication of the modified bacterium (p. 3, lines 27-28). The modified bacterium also has one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of said interstrand corsslinks (p. 53, lines 21-23). The modified bacterium further has a nucleic acid sequence encoding the antigen operably linked to a promoter sequence directing expression of the antigen by the modified bacterium (p. 98, lines 1-8). The antigen is heterologous to said *Listeria monocytogenes* bacterium (p. 98, lines 1-8; p. 45, lines 1-4).

Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 20-21, 87, 106, 110-113, 118, 137, 141, and 143-147 are unpatentable under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Whether claim 142 is unpatentable under 35 U.S.C. 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Whether claims 20, 87, 106, 110-113 are unpatentable under 35 U.S.C. 112, first paragraph as not being enabled.

4. Whether claims 21, 118, 137, 141 and 143-147 are unpatentable under 35 U.S.C., first paragraph as not being enabled.

5. Whether claims 20-21, 87, 106, 110-113, 118, 137, 141 and 143-147 are unpatentable over claims 1-9-112 and 116-119 of copending U.S. Application Serial No. 11/502,836 on the grounds of nonstatutory obviousness-type double patenting.

Argument

1. Rejection of claims 20-21, 87, 106, 110-113, 118, 137, 141, and 143-147 under 35 U.S.C. 112, second paragraph as being indefinite

Appellants request that the rejection of claims 20-21, 87, 106, 110-113, 118, 137, 141, and 143-147 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (final Office Action mailed 5/6/09, p. 2), be withdrawn or reversed.

The Federal Circuit has stated that a claim is definite if one skilled in the art would understand the bounds of the claim when read in light of the specification. *Invitrogen Corp. v. Biocrest Mfrg, L.P.*, 424 F.3d 1374 (Fed. Cir. 2005). If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, the demands of 35 U.S.C. § 112 are satisfied. *Credle v. Bond*, 25 F.3d 1566; 30 USPQ2d 1911 (Fed. Cir. 1994). The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art. *Ibid.*, (emphasis added). The Federal Circuit has also stated that only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite. *Metabolite Laboratories, Inc., v. Laboratory Corp. Of America Holdings*, 370 F.3d 1354; 71 USPQ2d 1081 (Fed. Cir. 2004). Other Federal Circuit decisions have also emphasized this point. *Honeywell*

Int'l, Inc. v. Int'l Trade Comm., 341 F.3d 1332; 68 USPQ2d 1023 (Fed. Cir. 2003) ("If the court determines that a claim is not 'amenable to construction,' then the claim is invalid as indefinite").

While limitations of the specification will not be read into the claims, the Federal Circuit has been clear that the claims are to be interpreted in light of the specification of which they are a part. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967; 34 USPQ2d 1321 (Fed. Cir. 1995) (*in banc*), *aff'd*, 517 U.S. 370; 38 USPQ2d 1461 (1996). Claims need only apprise those skilled in the art as to their scope, and be as precise as the subject matter permits. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367; 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

In the present case it is alleged that in claims 20 and 21 it is unclear what is encompassed by "one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of said interstrand crosslinks." (final Office Action mailed 5/6/09, p. 2, lines 13-15). The rejection alleges that it is unclear what mutations would cause the claimed activity, or whether the same mutation is made in both genes, and demands that the specific mutation be recited in the claim (final Office Action mailed 5/6/09, pp. 2-3).

As explained in the case law cited above, the purpose of the definiteness requirement is to apprise those skilled in the art as to the scope of the claim (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*). The claims must have a meaning discernible to those of ordinary skill in the art. *Credle v. Bond.*

Here, the person of ordinary skill readily understands that (1) nucleotide excision repair in bacteria is mediated in part by the *uvrA* and *uvrB* genes, and (2) various types of mutations placed in the *uvrA* and *uvrB* genes are achievable and will have the effect recited in the claims, which is inhibition of excision repair of interstrand crosslinks induced by a psoralen. Persons of ordinary skill understand that deletion mutants may be convenient to use for this purpose. Various types of mutations, for example, point mutations, insertion mutations, and/or frame-shift mutations introducing a stop codon; removal of promoter or other key sequences; and partial deletion mutations, may all be used to achieve the same effect recited in the claims - inhibiting

excision repair. The legal issue is whether the person of ordinary skill reviewing the claim can understand the scope of the claim. Here, the person of ordinary skill readily understands that any of the above types of genetic mutations can be used for the same effect. That the claims do not recite any specific type of mutation does not, therefore, render the claims as lacking a discernible meaning to the person of ordinary skill.

The rejection also alleges that the claim is vague as to if the same mutation is made in both genes. The language of the claim clearly states that "one or more mutations" are made in "*uvrA* and *uvrB* genes" with the result of "inhibiting excision repair." The person of ordinary skill understands that the *uvrA* and *uvrB* genes are part of a constitutive excision repair system in bacteria, and thus mutations in either of these genes can inhibit excision repair of interstrand crosslinks introduced by a psoralen. See, e.g., specification, p. 52, lines 10-15; p. 53, lines 20-29. Thus the person of ordinary skill readily understands that the same mutation can be made in both genes, or that different mutations may be made in the two genes. For example, the same stop condon may be introduced into each gene; or each gene may be deleted in its entirety.

For the above reasons, Appellants respectfully submit that the rejected claims satisfy the definiteness standard of 35 U.S.C. 112, second paragraph, and request that the rejection be withdrawn or reversed.

2. Rejection of claim 142 under 35 U.S.C. 112, second paragraph as being indefinite

Appellants request that the rejection of claim 142 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite (final Office Action mailed 5/6/09, p. 3), be withdrawn or reversed.

The rejection alleges that claim 142 is indefinite for reciting the phrase "the bacterial gene expression of the bacterium is substantially unaffected by the interstrand crosslinks." (Office Action mailed 5/9/09, p. 3, line 4). It is alleged that it is not clear if the recited term is in reference to all of the genes expressed by the bacterium, the genes other than *uvrA* and *uvrB*, or only the genes *uvrA* and *uvrB*.

First, it is noted that claim 142 is dependent on claim 21, and therefore incorporates all of

the limitations of claim 21. Claim 21 specifically recites that the *uvrA* and *uvrB* genes have genetic mutations that inhibit excision repair of the interstrand crosslinks induced by the psoralen. Thus, the person of ordinary skill understands that *uvrA* and *uvrB* are mutated. Thus, the person of ordinary skill reviewing the claim understands that the term "bacterial gene expression of the bacterium is substantially unaffected by the interstrand crosslinks" refers to gene expression of the bacterium other than the modifications previously recited in the claim.

Furthermore, the claim must be read in light of the specification, and not in isolation. The specification provides at page 37, lines 4-8 that, in order to be "substantially unaffected," the microbial gene expression need not be completely active upon modification of the nucleic acid. It is only necessary that in a population of a microbe in which the nucleic acid is modified to attenuate replication, microbial gene expression is sufficiently active to provide an adequate level of expression of the desired protein by the microbe. For example, if the microbe contains a particular antigen that is to be used as a vaccine, adequate expression would be determined as the minimum level of expression that provides an effective protective or therapeutic immune response to the vaccine." As the rejected claim relates to a method of inducing an immune response in a host to an antigen, it is clear that "substantially unaffected" refers to a level of expression of that antigen by the bacterium which is sufficient to stimulate an immune response in a host (specification, p. 7, lines 23-26).

For the above reasons, Appellants respectfully submit that the rejected claim satisfies the definiteness standard of 35 U.S.C. 112, second paragraph, and request that the rejection be withdrawn or reversed.

3. 35 U.S.C. 112, first paragraph (enablement) for claims 20, 87, 106, and 110-113

Appellants request that the rejection of claims 20, 87, 106, and 110-113 under 35 U.S.C. 112, first paragraph, as allegedly failing to satisfy the enablement requirement (final Office Action mailed 5/6/09, p. 3), be withdrawn or reversed.

The enablement requirement of 35 U.S.C. 112, first paragraph requires that the specification of a patent teach those skilled in the art to make and use the invention without

"undue experimentation." *In re Vaeck*, 947 F.2d 488; 20 USPQ2d 1438 (Fed.Cir.1991). The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? This remains the appropriate legal standard. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The BPAI has stated that when rejecting a claim under the enablement requirement, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification, which includes providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. *Ex Parte Hellman*, 2008 WL 19299967 at *2-3; *In re Wise*, 2009 WL 1956252 at *4.

A. The rejected claims recite that a modified *Listeria monocytogenes* bacterium comprises "one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of the psoralen-induced interstrand crosslinks" introduced into the bacterium. The rejection alleges that the number of potential mutations that may be made in the *uvrA* and *uvrB* genes is great, and that there are large numbers of insertions and deletions that may be made in the polynucleotide sequence (Office Action mailed 5/9/09, p. 5). While conceding that the number of operative embodiments is likely to be high, the rejection nevertheless alleges there is a lack of guidance leading to them. (*Ibid* at p. 5, lines 17-21). The rejection further concedes that the level of skill in the art is high (*Id.*, p. 6, lines 1-2), but states the art is also complex. The rejection further alleges that knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. (*Id.*, p. 6, lines 4-7). Finally, the rejection alleges that the specification does not provide the skilled person with evidence as to which modifications and regions of *uvrA* and *uvrB* should be targeted for modification to produce an attenuated bacterium with the desired phenotype (Id., p. 7, lines 4-7).

As conceded in the rejection, the level of skill in the art is high (Office Action mailed 5/6/09, p. 6, line 2). Persons of ordinary skill in the art are readily familiar with the various

techniques in molecular biology for performing genetic manipulations, and have long had knowledge of the structure the entire *Listeria monocytogenes* genome. This includes an understanding of both the *uvrA* and *uvrB* genes, including the specific nucleotides encoding ATP-binding and zinc finger domains in *uvrA*, and nucleotides encoding ATP-binding and helicase domains in *uvrB*. Moreover, the skilled artisan is familiar with methods for the introduction of stop codons in order to inhibit expression of genes, methods for deletion of genes and control sequences such as promoters, *etc*.

The specification provides the skilled artisan with numerous examples for making and using the *Listeria monocytogenes* strains recited in the claimed methods. The specification discloses mutants with the *uvrA* and *uvrB* genes deleted (p. 56, lines 29-30). Example 7 at p. 89 of the specification teaches the person of ordinary skill how to create a *uvrA*B deletion mutant using the known technique of allelic exchange and also provides further references explaining the technique (Camilli et al., *Molecular Microbiology* 8:143-147 (1993)). Table 9 at p. 89 also teaches additional examples of such deletion being performed in other *Listeria monocytogenes* strains. It is emphasized that this example alone enables the claims as the Federal Circuit has stated that nonenablement is the failure to disclose any mode and does not depend on the applicant advocating a particular embodiment or method for making the invention. *Spectra-Physics, Inc. v. Coherent, Inc*., 827 F.2d 1524; 3 USPQ2d 1737 (Fed. Cir. 1987) (emphasis added), *cert. denied*, 484 U.S. 954 (1987); *Engel Industries, Inc. v. Lockformer Co*., 946 F.2d 1528; 20 USPQ2d 1300 (Fed. Cir. 1991) ("the enablement requirement is met if the description enables any mode of making and using the claimed invention") See also *Johns Hopkins Univ. v. Cellpro Inc.* 152 F.3d 1342, 1361 (Fed. Cir. 1998) (holding that the enablement requirement is met if the description enables any mode of making and using the invention.).

The rejection refers to the Bowie reference, and alleges that knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects (Office Action mailed 5/6/09, p. 6, lines 4-6). But unpredictability in making amino acid substitutions in a protein in which the structure-function relationship is unclear does not indicate unpredictability in the ability to disrupt the expression or function of a sequence, particularly in the present case where key

nucleotides in the *uvrA* and *uvrB* genes are known. Thus, Bowie is not relevant to the present claims. Persons of ordinary skill informed by the present specification with readily acknowlegde that other forms of mutation can be used, and that disruption of expression and/or function of a gene would most likely occur if certain manipulations are implemented such as, but not limited to, any of the following: a) deletion of the entire coding sequence; b) deletion of a majority of the coding sequence; c) generation of one or more stop codons early in the coding sequence; d) a deletion early in the coding sequence that generates a frame-shift mutation; e) an insertion early in the coding sequence that generates a frame-shift mutation; f) deletion of the promoter or other key control sequence; and g) deletion of both the promoter and the coding sequence of the gene. The effects of these mutations are predictable and can be implemented and confirmed using standard molecular biology techniques and without undue experimentation. Even the rejection tacitly admits this by stating that the number of operative embodiments is "likely to be high." (Office Action mailed 5/9/09, p. 5, line 20).

The person of ordinary skill recognizes this because the actual mutation utilized is not critical, and arrival at additional mutations is a matter of routine application of molecular biology techniques. It is emphasized that the test of enablement is not whether any experimentation is necessary but, if experimentation is necessary, whether it is undue. *Hybritech Inc. v. Monoclonal Antibodies, Inc*. Applicants respectfully submit the person of ordinary skill with resort to the specification would have been readily able to identify a wide variety of mutations for disrupting either expression of any target genes such as *uvrA* and *uvrB* and/or the functionality of the products of such genes. The rejection provides no supported assertion that a person of ordinary skill would not be able to apply the invention using a wide variety of mutations, and is based on no more than unsubstantiated allegations.

B. Claim 20 recites a method of preventing or treating a disease, with dependent claim 113 reciting that the disease is cancer. The rejection makes a general allegation that the claims are drawn to prevention and treatment of any disease and "there is no known HIV vaccine prevention to date." (Office Action mailed 5/9/09, p. 8, lines 6-7).

Such an allegation, however, fails to support a rejection on the basis of lack of

enablement and confuses the requirements of patentability with those for securing government approval to market a drug for human use. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). Such a rejection is based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that might be encountered in practice. As is often noted in the case law, such an argument does not present a sufficient basis for rejecting a claim under the enablement requirement. See, e.g., *In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956); *Ex Parte Hicks*, 2000 WL 33673734 at *3.

Furthermore, while the claims might encompass some inoperative embodiments, this is also not dispositive of a lack of enablement. For example, vaccines may also be unlikely to work if exposed to high temperatures, chemicals such as 8M urea, or extremes of pH, as harsh conditions such as these are not particularly hospitable to biological materials. But, as the Federal Circuit has pointed out in the context of enablement rejections, it is not the purpose of claims to exclude such potentially inoperative embodiments. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576-77; 224 USPQ 409, 414 (Fed. Cir. 1984) ("It is not a function of the claims to specifically exclude ... possible inoperative [embodiments]"). Applicants also note that what has been demonstrated "to date" is equally not dispositive, as all inventions present something that has not been done before. As stated in *In re Chilowsky*, "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

Claim 20 recites a method of preventing or treating a disease that comprises administering a vaccine. The specification states that the term vaccine refers to an agent given to stimulate an immune response, so that if the individual subsequently is exposed to the antigen in nature, the pre-formed immune response will increase the individual's ability to fight off the agent (specification, p. 29, line 29 – p. 30, line 3). Vaccine also refers to one given to an individual who already has a disease associated with the vaccine antigen, wherein the vaccine can elicit an immune response or boost the individual's existing immune response to the antigen to provide an increased ability to fight off the agent (specification, p. 30, lines 3-7). It is noted that the claims do not require that the individual is cured of the disease, and in many medical situations an individual receives vaccines or is otherwise treated for a disease without ever

actually being successfully cured of the disease. Nevertheless vaccines can provide an important benefit during treatment of a wide variety of diseases. One does not need to "cure" a disease in order to enable its treatment with an agent, as the rejection would seem to (incorrectly) assert. Indeed, even in the Examiner's example of HIV, individuals are currently being "successfully" treated without curing the disease.

With respect to treating or preventing cancer, Example 10 of the specification provides a specific example and teaches how to prepare the microbe to be included in the vaccine. The Example also teaches incorporation of prokaryotic expression cassettes encoding human tumor antigen(s) into the microbe of the vaccine. Methods of administering the vaccine are also taught. Further, with respect to "preventing," it is taught that the vaccine can be given to patients that have had tumors surgically removed or who have been treated with radiation or chemotherapy methods in order to reduce or eliminate residual tumors or reduce the risk of a recurrence of the cancer (specification, p. 104, lines 27-30), thus preventing cancers, or as a prophylactic treatment for an individual with an increased risk of contracting certain cancers, either due to environmental condition or genetic predisposition (p. 104, line 30 – p. 105, line 2).

Examples 15 and 16 provide specific examples of using the methods of the invention to treat lung metastases (e.g., cancer) in a melanoma model system. Example 15 teaches C57B1/6 mice injected with melanoma tumor cells to establish lung metastases. The data presented in Example 15 and illustrated in Figures 19A-C show that psoralen/UVA treated *uvrA*B mutants were administered as a therapeutic vaccine, resulting in significantly reduced lung metastases and extended survival compared to mice that did not receive the vaccine, and thus prevented further cancers from forming. Example 1 states that parent strain DP-L4029*uvrA*B used in this example was deposited with ATCC on October 3, 2003 and assigned PTA-5563 (specification, p. 94, lines 24-25), thus placing this strain into the hands of the person of ordinary skill. In Example 16 CT26 tumor cells modified to express a human antigen were injected into Balb/c mice to establish lung metastases. In combination with the data presented in Example 16, Figure 20A-D show that mice treated according to the invention had significantly reduced lung metastases and extended survival, thus preventing cancers from forming. Example 17 teaches the use of fluorescence microscopy to show *Listeria monocytogenes* being taken up and

distributed within antigen presenting cells, using dendritic cell line DC 2.4. Example 20 teaches that mice treated according to the invention showed a significantly higher ability to lyse cells expressing a target antigen.

While the rejection alleges that the claims are broadly drawn, the claimed invention can be practiced throughout its scope without undue experimentation because the person of ordinary skill with reference to the specification understands its application and need use no more than conventional techniques to apply it. *Ajinomoto Co., Inc., v. Archer-Daniels-Midland Co.*, 228 F.3d 1338; 56 USPQ2d 1332 (Fed. Cir. 2000). Thus, the specification provides working examples that remove unpredictability from the practice of the invention. Claim 20 is drawn to a method comprising the administration of *Listeria* bacteria. Vaccine compositions may be used to stimulate immunity (mediated by B-cells, T-cells, or both) to an antigen, and/or may be intended to stimulate the innate immune system, which comprises cells and mechanisms that defend the host in a non-specific manner. The innate system recognizes, and responds to, diseases in a generic way and provides immediate short-term defense. It is well established that bacteria, including *Listeria*, stimulate the innate immune system, and can also be used to deliver foreign antigens to stimulate an immune response.

C. In view of the nature of the invention and the art, the level of skill in the art, the quantity of experimentation necessary, the amount of guidance provided in the specification, and the working examples provided, including the specific examples relating to the treatment of diseases such as cancer, the rejection fails to establish that it would require undue experimentation to make and use the claimed invention within the scope of the claims. In fact, no more than routine experimentation would be required to apply the invention throughout its scope. The person of ordinary skill understands that an immune response can be triggered to an antigen according to the invention and that this could be used to provide prevention or treatment of a disease associated with that antigen.

For the above reasons, Appellants respectfully submit that the rejected claims satisfy the enablement standard of 35 U.S.C. 112, second paragraph, and request that the rejection be withdrawn or reversed.

4. 35 U.S.C. 112, first paragraph (enablement) for claims 21, 118, 137, 141, and 143-147

Appellants request that the rejection of claims 21, 118, 137, 141, and 143-147 under 35 U.S.C. 112, first paragraph, as allegedly failing to satisfy the enablement requirement (final Office Action mailed 5/6/09, p. 3), be withdrawn or reversed.

The enablement requirement of 35 U.S.C. 112, first paragraph requires that the specification of a patent teach those skilled in the art to make and use the invention without "undue experimentation." *In re Vaeck*, 947 F.2d 488; 20 USPQ2d 1438 (Fed.Cir.1991). The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? This remains the appropriate legal standard. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

A. The rejected claims recite that the modified *Listeria monocytogenes* bacterium have one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of the psoralen-induced interstrand crosslinks. The rejection alleges that the number of potential mutations that may be made in the *uvrA* and *uvrB* genes is great, and that there are large numbers of insertions and deletions that may be made in the polynucleotide sequence (Office Action mailed 5/9/09, p. 5). While conceding that the number of operative embodiments is likely to be high, the rejection nevertheless alleges there is a lack of guidance leading to them. (*Ibid* at p. 5, lines 17-21). The rejection further concedes that the level of skill in the art is high (*Id.*, p. 6, lines 1-2), but states the art is also complex. The rejection further alleges that knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. (*Id.*, p. 6, lines 4-7). Finally, the rejection alleges that the specification does not provide the skilled person with evidence as to which modifications and regions of *uvrA* and *uvrB* should be targeted for modification to produce an attenuated bacterium with the desired phenotype (Id., p. 7, lines 4-7).

As conceded in the rejection, the level of skill in the art is high (Office Action mailed

5/6/09, p. 6, line 2). Persons of ordinary skill in the art are readily familiar with the various techniques in molecular biology for performing genetic manipulations, and have long had knowledge of the structure the entire *Listeria monocytogenes* genome. This includes an understanding of both the *uvrA* and *uvrB* genes, including the specific nucleotides encoding ATP-binding and zinc finger domains in *uvrA*, and nucleotides encoding ATP-binding and helicase domains in *uvrB*. Moreover, the skilled artisan is familiar with methods for the introduction of stop codons in order to inhibit expression of genes, methods for deletion of genes and control sequences such as promoters, *etc*.

The specification provides the skilled artisan with numerous examples for making and using the *Listeria monocytogenes* strains recited in the claimed methods. The specification discloses mutants with the *uvrA* and *uvrB* genes deleted (p. 56, lines 29-30). Example 7 at p. 89 of the specification teaches the person of ordinary skill how to create a *uvrA*B deletion mutant using the known technique of allelic exchange and also provides further references explaining the technique (Camilli et al., *Molecular Microbiology* 8:143-147 (1993)). Table 9 at p. 89 also teaches additional examples of such deletion being performed in other *Listeria monocytogenes* strains. It is emphasized that this example alone enables the claims as the Federal Circuit has stated that nonenablement is the failure to disclose any mode and does not depend on the applicant advocating a particular embodiment or method for making the invention. *Spectra-Physics, Inc. v. Coherent, Inc*., 827 F.2d 1524; 3 USPQ2d 1737 (Fed. Cir. 1987) (emphasis added), *cert. denied*, 484 U.S. 954 (1987); *Engel Industries, Inc. v. Lockformer Co*., 946 F.2d 1528; 20 USPQ2d 1300 (Fed. Cir. 1991) ("the enablement requirement is met if the description enables any mode of making and using the claimed invention") See also *Johns Hopkins Univ. v. Cellpro Inc.* 152 F.3d 1342, 1361 (Fed. Cir. 1998) (holding that the enablement requirement is met if the description enables any mode of making and using the invention.).

The rejection refers to the Bowie reference, and alleges that knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects (Office Action mailed 5/6/09, p. 6, lines 4-6). But unpredictability in making amino acid substitutions in a protein in which the structure-function relationship is unclear does not indicate unpredictability in the ability to

disrupt the expression or function of a sequence, particularly in the present case where key nucleotides in the *uvrA* and *uvrB* genes are known. Thus, Bowie is not relevant to the present claims. Persons of ordinary skill informed by the present specification with readily acknowlegde that other forms of mutation can be used, and that disruption of expression and/or function of a gene would most likely occur if certain manipulations are implemented such as, but not limited to, any of the following: a) deletion of the entire coding sequence; b) deletion of a majority of the coding sequence; c) generation of one or more stop codons early in the coding sequence; d) a deletion early in the coding sequence that generates a frame-shift mutation; e) an insertion early in the coding sequence that generates a frame-shift mutation; f) deletion of the promoter or other key control sequence; and g) deletion of both the promoter and the coding sequence of the gene. The effects of these mutations are predictable and can be implemented and confirmed using standard molecular biology techniques and without undue experimentation. Even the rejection tacitly admits this by stating that the number of operative embodiments is "likely to be high." (Office Action mailed 5/9/09, p. 5, line 20).

The person of ordinary skill recognizes this because the actual mutation utilized is not critical, and arrival at additional mutations is a matter of routine application of molecular biology techniques. It is emphasized that the test of enablement is not whether any experimentation is necessary but, if experimentation is necessary, whether it is undue. *Hybritech Inc. v. Monoclonal Antibodies, Inc*. Applicants respectfully submit the person of ordinary skill with resort to the specification would have been readily able to identify a wide variety of mutations for disrupting either expression of any target genes such as *uvrA* and *uvrB* and/or the functionality of the products of such genes. The rejection provides no supported assertion that a person of ordinary skill would not be able to apply the invention using a wide variety of mutations, and is based on no more than unsubstantiated allegations.

B. Claim 21 recites a method of inducing an immune response in a host that comprises administering a vaccine. The specification states that the term vaccine refers to a vaccine given to stimulate an immune response so that if the individual subsequently is exposed to the antigen in nature, the pre-formed immune response will increase the individual's ability to fight off the agent (specification, p. 29, line 29 – p. 30, line 3. Vaccine also refers to one given

to an individual who already has a disease associated with the vaccine antigen, wherein the vaccine can elicit an immune response or boost the individual's existing immune response to the antigen to provide an increased ability to fight off the agent (specification, p. 30, lines 3-7). It is noted that the claims do not require that the individual is cured of the disease, and in many medical situations vaccines are delivered to raise an immune response to a disease-associated antigen without "curing" the disease. Therefore, one does not need to cure a disease in order to enable the rejected claims, as the rejection would seem to (incorrectly) assert.

It is worth noting that a similar enablement rejection was recently reversed in *In re Wise*, 2009 WL 1956252, which involved a claim to a vaccine composition for inducing an immune response to a pathogen. The examiner in *Wise* had contended that the claims were enabled only as to the specific working examples described in the specification, and further interpreted the claims to require that the vaccine provide protective immunity. The Board reversed, finding that while the technology was in its infancy, there were no barriers to its development (*Ibid* at *4), and that the prior art had indicated the vaccine technology was adequate for eliciting an immune response. The Board also found the claims did not require achieving protective immunity and that the Examiner had therefore not met the burden of establishing lack of enablement for the full scope of the claims (*Id.* at *4).

A similar result was obtained in *Ex Parte Hellman*, 2008 WL 1929967. In this case claims to an immunogenic polypeptide comprising a self IgE amino acid segment were rejected as not enabled. The claims recited that the immunogenic polypeptide was effective to induce an anti-self IgE response. The examiner had interpreted the claims to also require that the induced immune response must be effective to treat an IgE related disease. The Board reversed, finding that the claims recited no such requirement and that the Examiner had not fulfilled the requirements for rejecting a claims as not enabled, which requires providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. (*Ibid* at *3).

In the present case, the specification contains numerous examples clearly demonstrating the enablement of claim 21 and its dependent claims. Examples 1-2 teach how to perform psoralen treatment of *Listeria* strains providing attenuation of proliferation while maintaining

expression of a model antigen - chicken ovalbumin (OVA). Persons of ordinary skill in the art realize that expression of OVA antigen in a host will induce an immune response, and that this result can be extrapolated to other antigens, including disease-related antigens. Example 8 teaches the insertion of antigen expression cassettes into the genomes of *Listeria* strains, and how to express a heterologous protein or antigen relevant to malignant or infectious disease. Example 8 further teaches expression in *Listeria* of OVA model antigen as a fusion partner with the amino-terminal half of the Listeriolysin O (LLO) protein that includes the secretion signal and PEST sequence.

Examples 15 and 16 provide specific examples of using the methods of the invention to treat lung metastases in a melanoma model system. Example 15 teaches C57B1/6 mice injected with melanoma tumor cells to establish lung metastases. The data presented in Example 15 and illustrated in Figures 19A-C show that psoralen/UVA treated *uvrA*B *Listeria* mutants (strain DP-L4029-OVA) expressing heterologous antigen were administered as a therapeutic vaccine, resulting in significantly reduced lung metastases and extended survival compared to mice that did not receive the vaccine, and thus prevented further cancers from forming. Example 1 states that parent strain DP-L4029*uvrA*B used in this example was deposited with ATCC on October 3, 2003 and assigned PTA-5563 (specification, p. 94, lines 24-25), thus placing this strain into the hands of the person of ordinary skill. Example 16 describes CT26 tumor cells (which express AH1 antigen) modified to express a human antigen injected into Balb/c mice to establish lung metastases. AH1A5 antigen is endogenous to the mice, such that any immunization effect would be breaking immune tolerance in the mice, resulting in significantly reduced lung metastases and extended survival. In combination with Table 18 and the data presented in Example 16, Figure 20A-D show that mice treated according to the invention had significantly reduced lung metastases and extended survival, thus preventing cancers from forming and demonstrating to a person of ordinary skill induction of an immune response. Example 20 teaches that mice treated according to the invention showed a significantly higher ability to lyse cells expressing a target antigen.

In contrast to the evidence of record indicative of enablement, the rejection is based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with

various difficulties that might be encountered in practice. As is often noted in the case law, such an argument does not present a sufficient basis for rejecting a claim under the enablement requirement. See, e.g., *In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956); *Ex Parte Hicks*, 2000 WL 33673734 at *3.

Furthermore, while the claims might encompass some inoperative embodiments, this is also not dispositive of a lack of enablement. For example, vaccines may also be unlikely to work if exposed to high temperatures, chemicals such as 8M urea, or extremes of pH, as harsh conditions such as these are not particularly hospitable to biological materials. But, as the Federal Circuit has pointed out in the context of enablement rejections, it is not the purpose of claims to exclude such potentially inoperative embodiments. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576-77; 224 USPQ 409, 414 (Fed. Cir. 1984) ("It is not a function of the claims to specifically exclude ... possible inoperative [embodiments]"). Applicants also note that what has been demonstrated "to date" is equally not dispositive, as all inventions present something that has not been done before. As stated in *In re Chilowsky*, "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

C. In the present case, persons of ordinary skill reviewing the data presented in the specification understand that the results described were obtainable because administration of the vaccine of the invention induced an immune response in the host organism. Claim 21 requires no more. The specification provides actual working examples relating to inducing an immune response in a host to an antigen throughout the scope of the claim, as well as many examples of how to create the modified *Listeria monocytogenes* bacterium utilized in the method. With reference to these examples and the additional information provided in the specification the person of ordinary skill understands that a wide variety of desirable antigens can be expressed in the method with no more than routine experimentation. Therefore, the cited claims are clearly enabled by the specification.

5. Double Patenting

Appellants request that the rejection of claims 20-21, 87, 106, 110-113, 118, 137, 141 and 143-147 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9-112 and 116-119 of copending U.S. Application Serial No. 11/502,836 (the '836 Application) be withdrawn or reversed.

This issue was presented for the first time in the final rejection mailed 5/6/09. Appellants note that no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. In the event that other rejections of the present claims are successfully overcome by the current appeal, withdrawal of the instant provisional rejection would be appropriate. Applicants will submit a terminal disclaimer in the present case over the '836 Application in the event that the claims in the '836 Application issue prior to the claims in the present case.

In the final rejection mailed 5/6/09, reference was also made to Application Serial No. 10/553,809, but no rejection was made (Office Action mailed 5/6/09, p. 11, line 9). It is believed this reference was in error and the Examiner intended to refer to the '836 Application. Nevertheless, Application Serial No. 10/553,809 is both abandoned and unrelated to the present case and cannot serve as the basis of any proper double patenting rejection.

For the above reasons, Appellants respectfully request that the rejection be withdrawn or reversed.

Closing

In view of the above, Appellants respectfully request that the rejections be reversed and that the claims allowed to issue.

Respectfully submitted,

Date: 21 April 2010
BIOTECHNOLOGY LAW GROUP
12707 High Bluff Drive
Suite 200
San Diego, CA 92130
Customer Number 35938

By: /Michael A. Whittaker/
Michael A. Whittaker
Reg. No. 46,230
Tel. No. (619) 203-3186
Fax No. (858) 683-0390

Claims Appendix

20. A method of preventing or treating a disease in a host, comprising administering to the host an effective amount of a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the modified bacterium comprising (i) psoralen-induced interstrand crosslinks introduced between the strands of genomic DNA double helix, said interstrand crosslinks inhibiting replication of said modified bacterium, (ii) one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of said interstrand crosslinks, and (iii) a nucleic acid sequence encoding a polypeptide heterologous to said *Listeria monocytogenes* bacterium operably linked to a promoter sequence directing expression of the heterologous polypeptide by the modified bacterium.

21. A method of inducing an immune response in a host to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified *Listeria monocytogenes* bacterium, wherein the modified bacterium comprises (i) psoralen-induced interstrand crosslinks introduced between the strands of genomic DNA double helix, said interstrand crosslinks inhibiting replication of said modified bacterium (ii) one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of said interstrand crosslinks, and (iii) a nucleic acid sequence encoding the antigen operably linked to a promoter sequence directing expression of the antigen by the modified bacterium, wherein said antigen is heterologous to said *Listeria monocytogenes* bacterium.

87. The method of claim 20, wherein the interstrand crosslinks are introduced by reaction with 4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen activated by irradiation.

106. The method of claim 20, wherein the genetic mutations in *uvr* gene(s) comprise deletions in the *uvr*A and *uvr*B, genes such that the modified bacterium does not produce functional *uvrA* and *uvrB* gene products.

110. The method of claim 20, wherein the vaccine further comprises a pharmaceutically acceptable carrier or an adjuvant.

111. The method of claim 20, wherein the bacterial gene expression of the bacterium is substantially unaffected by the interstrand crosslinks.

112. The method of claim 20, wherein the disease is an infectious disease.

113. The method of claim 20, wherein the disease is cancer.

118. The method of claim 21, wherein the interstrand crosslinks are introduced by reaction with 4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen activated by irradiation.

137. The method of claim 21, wherein the genetic mutations in *uvr* gene(s) comprise deletions in the *uvr*A, and *uvr*B genes such that the modified bacterium does not produce functional *uvrA* and *uvrB* gene products.

141. The method of claim 21, wherein the vaccine further comprises a pharmaceutically acceptable carrier or an adjuvant.

142. The method of claim 21, wherein the bacterial gene expression of the bacterium is substantially unaffected by the interstrand crosslinks.

143. The method of claim 21, wherein the antigen is a tumor antigen.

144. The method of claim 143, wherein the tumor antigen is mesothelin, SPAS-1, proteinase-3, SP-17, gp100, PAGE-4, TARP, Her-2/neu, WT-1, NY-ESO-1, PSMA, K-ras, survivin, mcm-2, or CEA, or an antigen derived from mesothelin, SPAS-1, proteinase-3, SP-17, gp100, PAGE-4, TARP, Her-2/neu, WT-1, NY-ESO-1, PSMA, K-ras or CEA.

145. The method of claim 21, wherein the antigen is an infectious disease antigen.

146. The method of claim 145, wherein the antigen is derived from a Human Immundeficiency Virus or a hepatitis virus.

147. The method of claim 146, wherein the antigen is derived from hepatitis C virus.

Evidence Appendix

None

Related Proceedings Appendix

None